REMARKS

Reconsideration is respectfully requested. Claims 7, 8 and 9 have been amended. Claims 1-6, 10, and 18-20 were canceled in a previous amendment. Claims 13, 15-17 and 21-25 are canceled in the present amendment. After entry of this amendment, claims 7-9, 11-12, and 14 will be pending.

Withdrawal of Objections and Rejections

Applicants respectfully thank the Examiner for withdrawing the previous objections and/or rejections.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 15

The Examiner has rejected claim 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out or distinctly claim the subject matter which the applicant regards as the invention.

Without acquiescing to the Examiner's rejection, Applicants have cancelled claim 15. Accordingly, this ground for rejection is moot. Applicants respectfully request that this ground for rejection be withdrawn.

"Therapeutically Active Region" and "Less Therapeutically Active Region"

The Examiner has rejected claims 1-5 and 16 for using the phrases "therapeutically active region" and "less therapeutically active region."

Without acquiescing to the Examiner's rejection, Applicants have cancelled claims directed to therapeutically active regions. Accordingly, this ground for rejection is now moot. Applicants respectfully request that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. § 103

The Examiner states that claims 7-9, 11-17, and 21-25 are rejected under 35 U.S.C. § 103 over Pouletty et al. (U.S. Patent No. 6,103,223) in view of Oppenhelm et al. (U.S. Patent No. 5,837,247). The Examiner's arguments, however, are based on Pouletty et al. and Breton et al. Therefore, we assume that Oppenhelm et al. was erroneously mentioned, and the rejection is made over Pouletty et al. (US 6,103,223) in view of Breton et al.

As stated in the prior response and reiterated here, 35 U.S.C. § 103(a) requires that "...differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The prima facie case must satisfy three requirements: 1) the references must teach or suggest all the claim limitations; 2) the prior art combined with general knowledge must include a suggestion or incentive to modify or combine the references; and 3) the modification or combination must have a reasonable chance of success.

Claims 7-9, 11-17, and 21-25

Independent claim 7 is directed to a method of protecting a therapeutic peptide from peptidase degradation by modifying the peptide by coupling it to a reactive group, forming a covalent bond between the reactive group and a reactive functionality on albumin, and analyzing the stability of the peptide-albumin conjugate.

Claims 8-9, 11-12 and 14 depend from claim 7.

Claims 13, 15-17 and 21-25 have been cancelled.

The Cited References

Pouletty et al. disclose conjugating a compound to a mobile blood component to remove undesirable entities from the blood, or to increase the half-life of the compound. Pouletty et al. are devoid of any teaching, mention, or hint of protecting the peptide from peptidase degradation, conjugation to albumin, or analyzing the stability of the peptide-albumin conjugate towards peptidase degradation and confirming that the peptide-albumin conjugate has a higher stability than the therapeutic peptide.

Breton et al. disclose prolonging half-life of the 411 amino acid pro-urokinase protein by covalently bonding it to a chemically modified, non-native, denatured, inactive human serum albumin.

The Examiner's Rejection

The Examiner alleges, in the absence of evidence, that Pouletty et al. disclose a method of protecting a therapeutic peptide from peptidase degradation. The Examiner goes on to argue that Pouletty et al. teach a method of increasing the half-life of a therapeutic peptide *in vivo*. The Examiner alleges that Pouletty et al. disclose a method of analyzing the peptide-blood component admits that Pouletty et al. does not expressly teach the step of analyzing the blood component for resistance to peptidase degradation.

The Examiner further argues that Breton et al. teaches that conjugation of a peptide to albumin protects the conjugate from peptidase, and argues that this results in an increased half-life. The Examiner fails to note that the pro-urokinase is a 411 amino acid protein, not the 3-50 amino acid therapeutic peptide of the present application, and that the method taught by Breton et al. conjugates the pro-urokinase to a modified, denatured, inactive, non-native albumin mutant.

The Cited References Distinguished

The Examiner fails to make a prima facie case of obviousness on multiple grounds. Specifically, the cited prior art references a) fail to teach or suggest all claim limitations of the present invention, b) fail to provide motivation or suggestion for one of ordinary skill in the art to make the claimed invention, and c) fail to disclose any information indicating that one of ordinary skill in the art would have a reasonable chance of success. Accordingly, the subject matter of the instant claims as a whole would not have been obvious to one of skill in the art at the time the invention was made.

First, the cited references fail to teach every limitation of the present claims. Pouletty et al. do not mention, suggest or imply protecting a therapeutic peptide from peptidase degradation. Instead, Pouletty et al. disclose the conjugation of a compound to a mobile component for two different purposes: i) binding undesirable entities circulating in the blood or ii) extending the half-life of the compound. The ultimate effect of the conjugation in both purposes is to modify the pharmacokinetic profile of the resulting conjugated compound to be closer to that of the blood component, and eventually allow the biological elimination of the conjugated compound. Pouletty et al., however, lacks any teaching of protecting a therapeutic peptide from peptidase degradation.

In addition, as the Examiner admits, Pouletty et al. fail to teach a step of analyzing the stability of a therapeutic peptide- albumin conjugate towards peptidase degradation and confirming that the peptide-albumin conjugate has a higher stability than the therapeutic peptide. In the present invention, different modified peptides are designed by analyzing their stability towards peptidase degradation, since only the modified peptides having the combination of an increased stability to peptidase degradation and a satisfactory therapeutic activity are selected. Pouletty et al., by contrast, fail to disclose any criterion for determining the position of attachment of the compound to the anchor. The present method, which is specifically restricted to peptides comprising between 3 and 50 amino acids, has been developed to ensure that: 1) the therapeutic activity of the unmodified peptide is substantially retained and 2) the peptidase degradation of the peptide is dramatically reduced. The focus of Pouletty et al. is on the biological elimination of the resulting conjugate to the blood component. Criteria for analyzing the stability of a therapeutic peptide conjugate towards peptidase degradation and confirming that the peptide conjugate has a higher stability than the therapeutic peptide are not even remotely disclosed.

Breton et al. do not cure deficiencies of Pouletty et al. Breton et al. teach the formation of a chemical conjugate comprising a 411 amino acid pro-urokinase derivative and chemically modified, non-native, and therefore inactive serum albumin mutant. Breton et al. make their conjugate by the following steps: a) breaking all the disulfide bridges of the albumin with diisopropylfluorophosphate; b) blocking all the accessible groups SH, including the ones resulting from step (a), by alkylation with iodoacetamide; c) coupling the group succinimidyl 3-(2-pyridylthio)propionate to albumin; and d) allowing the reaction of the cysteine of a fragment of pro-

urokinase (the cysteine residue was previously added at the N-terminal of the fragment of pro-urokinase). The resulting amino acid chain of albumin in the chemical conjugate of Breton et al. shares no biochemical characteristics with the correctly folded and functional native albumin. Breton et al. further teach the complete denaturation of the albumin by opening the disulfide bridges and alkylating the resulting SH groups. The resulting conformation is not the folded and compact native albumin molecule, but rather a denatured, inactive molecule that only shares a similar sequence with albumin, but does not have the structure or activity of native albumin.

In contrast to Breton et al., the present claims are directed to forming the peptide-albumin conjugate *in vivo* or *ex vivo* using non-denatured albumin. The Specification discusses *in vivo* and *ex vivo* conjugation at page 87, lines 5-14. *In vivo* conjugation is clearly limited to native albumin, since native albumin is the only albumin present *in vivo* that can be conjugated to the therapeutic peptide. The Specification discusses *ex vivo* conjugation to albumin in the context of albumin contained in buffered solutions such as blood, serum, or saline that are necessary to promote correct folding and maintain albumin activity. For example, at page 87, lines 6-8, the Specification states that "for ex *vivo* covalent bond formation, the modified therapeutic peptide ...is added to blood, serum or saline solution containing human serum albumin." At page 87, lines 10-12, the Specification states "in a preferred format, the therapeutic peptide is modified with maleimide and ...is reacted with human serum albumin in saline solution." Clearly, albumin, as contemplated by the Specification, does not include the extensively modified and denatured albumin of Breton et al.

Second, the references fail to provide the requisite motivation or suggestion to combine their teachings to perform the claimed method. One would not be motivated to react a blood component cited in Pouletty et al. via the method taught by Breton et al. Pouletty et al. fail to suggest, mention, or hint at protecting a therapeutic peptide comprising between 3 and 50 amino acids from peptidase degradation, analyzing the stability of the peptide-albumin conjugate towards peptidase degradation, or confirming that the peptide-albumin conjugate has a higher stability than the therapeutic peptide. Breton et al. only teach conjugation of pro-urokinase, a 411 amino acid plasminogen activator, after extensive modification and denaturization of a non-native albumin mutant. At most, one of skill in the art would be motivated to a) design a non-native mutant of albumin, b) denature the non-native albumin mutant, rendering it incorrectly folded and inactive, and c) chemically modify the non-

native, denatured albumin mutant, and d) react the non-native, denatured, chemically modified albumin mutant with a large protein.

Moreover, Breton et al. do not provide any suggestion or mention of a way to protect therapeutic peptides comprising between 3 and 50 amino acids from peptidase degradation. The pro-urokinase identified by Breton et al. is a 411 amino acid plasminogen activator, not a peptide comprising between 3 and 50 amino acids, as required by the claims. Therefore, Breton et al. do not provide any suggestion that conjugating pro-urokinase, or any other peptide, at the surface of an intact molecule of albumin would lead to the protection of pro-urokinase, other large proteins, or peptides comprising between 3 and 50 amino acids, from peptidase degradation.

Third, one of ordinary skill in the art would not have a reasonable expectation of success in altering the teachings of Pouletty et al. to make the present invention. Changing the position of attachment of the reactive group is likely to affect the activity and the stability. The way that the activity and the stability are affected is not predictable. The method claimed in the present application is designed to allow one skilled in the art to select the best combination between the activity and the stability. In some circumstances, it can be desirable to select a conjugate exhibiting a modest activity and a higher stability towards peptidases. In other circumstances, it may be preferable to have a higher activity and a lower stability towards peptidases.

Pouletty et al. fail to provide any reasonable expectation of protecting a therapeutic peptide from peptidase degradation by the claimed method. Pouletty et al. make no reference to protecting peptides from peptidase degradation. Further, Pouletty et al. fail to mention analyzing the stability of the albumin conjugate towards peptidase degradation and confirming the peptide-albumin conjugate has a higher stability than the therapeutic peptide. Since Pouletty et al. fail to mention, suggest, or hint at either limitation, one of skill in the art would not have a reasonable expectation of success in achieving the claimed methods based on Pouletty et al.

Further, based on the teachings of Breton et al., one of ordinary skill would not have a reasonable expectation of success in modifying the teachings of Pouletty et al. to achieve the claimed method. Breton et al. teach extending the life-time of a full length pro-urokinase protein not by reacting pro-urokinase with native albumin, but by reacting pro-urokinase with an extensively modified, denatured, inactive, non-native albumin derivative. The site of conjugation in Breton et al. is a non-native terminal cysteine residue added by Breton et al. The internal di-sulfide bonds of

the albumin molecule as taught by Breton et al. are all broken prior to reaction with pro-urokinase, thus denaturing the albumin and rendering the molecule inactive. The "albumin" taught by Breton et al. thus a) does not have the sequence of albumin active *in vivo*, and b) does not have the structure of albumin that is active *in vivo*.

Further, Breton et al. do not provide a reasonable expectation that pro-urokinase is protected from peptidase degradation. Rather, Breton et al only speculate, in the Abstract of the reference, that pro-urokinase may be protected from degradation, but provide no supporting evidence. Mere speculation in the absence of evidence does not provide a reasonable expectation of success. One of skill in the art would therefore not have a reasonable expectation of success in protecting a large protein such as pro-urokinase, let alone a therapeutic peptide comprising between 3 and 50 amino acids, from peptidase degradation.

The references, in combination, fail to teach every limitation of the present claims, fail to provide the requisite motivation or suggestion to combine their disclosures, and fail to provide a reasonable expectation of success in achieving the claimed method. The Examiner has therefore failed to provide a prima facie case for obviousness. Applicants respectfully request that this ground for rejection be withdrawn.

Information Disclosure Statement

Applicants have filed herewith a Supplemental Information Disclosure Statement. The document cited therein was cited in an examination report dated July 11, 2003, with respect to the corresponding European national stage application of WO 99/24462.

Conclusion

In light of the above amendments and remarks, Applicant believes that this case is now in condition for allowance. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any

required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **500862002300**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October , 2003

DRAFT

Respectfully submitted,

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